Haemost., 1992(3):310-314); and an abstract by Xu et al., (*J. Histochem. Cytochem.*, 1994(10):1365-1376). A check in the amount of $55.00, the fee for a one month extension of time for a small entity, is also enclosed. It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-1868

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Claims

3. (amended) The method of claim 1 wherein the [antibody] inhibitor is administered systemically.

Remarks

Claims 1-9, 11-13, and 19-21 are pending. Claims 14-16 have been canceled by the Examiner under 1214.06 of the M.P.E.P. based on the decision by the Board of Appeals.

Claim 3 has been amended to correct antecedent basis.

The present invention is directed to methods for reducing blood loss from microvascular bleeding due to wounds caused by surgery or trauma. The methods and compositions are particularly useful in treating microvascular bleeding from skin graft donor sites, burns, bleeding

liver surfaces, and inflamed visceral surfaces. Reduction of blood loss from microvascular bleeding depends upon effectively attenuating or ceasing anticoagulation. The invention is not the discovery of the coagulation process, or components thereof. It is the discovery that it is possible to inhibit a single component of the process and thereby inhibit microvascular bleeding. The Board of Appeals has already determined the claimed method is both enabled and novel and non-obvious over the prior prior art. The only issue at this time is whether or not applicant has complied with the written description requirement.

Claims 1-6, 11-13, and 19 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which allegedly was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention. Applicant respectfully traverses this rejection.

The Claims

The claims to the process wherein the inhibitor of microvascular bleeding is an antibody to protein C were not rejected. The remaining claims were rejected based on alleged failure to describe the claimed subject matter in a way that demonstrated the applicant was in possession of the claimed invention. It is important to note in this case what is claimed, and what is not claimed. Applicant is not claiming a composition. Applicant is claiming a method. Applicant has demonstrated with an example using an antibody to protein C that the claimed method works. Applicant has described a number of other components of the coagulation pathway that can be inhibited in the claimed method other than protein C. Just as the antibody to protein C was known to those skilled in the art at the time the application was filed, so were inhibitors of

these other components of the coagulation process. What was not known was the method. This is extremely important in analyzing the claims under 35 U.S.C. 112.

Claim 1 is drawn to a method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

It was known at the time this application was filed that one could inhibit protein C in the anticoagulation process directly (i.e., an antibody to protein C), or indirectly, via antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

As noted above, the Board of Appeals has already found this claim enabled and novel and inventive. The proteins in the method are known, as are inhibitors, as more fully demonstrated by the accompanying abstracts.

Claim 2 defines the anticoagulant as protein C.

Claim 3 wherein the inhibitor is administered systemically. Claim 4 defines the method where the inhibitor is administered topically. Claim 19 further comprises the step of topically administering a coagulant at the site of bleeding. Both types of methods of administration were known.

Claim 5 is the method of claim 1 further comprising topically administering at the site of the bleeding a coagulant. Many coagulants such as thrombin were known - indeed, these are the

prior art compositions used to inhibit microvascular bleeding. Claim 6 defines the coagulant as thrombin or tissue thromboplastin.

Claims 7-10, 20 and 21 are not rejected under 112. These define the inhibitor as an antibody to protein C.

Claims 11-13 define the patient to be treated (claim 11, burn patient; claim 12, patient with tissue or skin grafts; claim 13, patient with cerebral contusions).

The Legal Standard

The Applicant respectfully submits that the inquiry into whether or not there is an adequate written description is not performed in a vacuum. "Knowledge of one skilled in the art is relevant to meeting [the written description] requirement." *Enzo Biochem, Inc. v. Gen-Probe*, Docket No. 01-1230 (Fed. Cir. Apr. 2, 2002) (slip op.). This fact has implications not only for validity challenges, but also for patent prosecution. *See In re Alton*, 76 F.3d 1168, 1174-75 (Fed. Cir. 1996). In its Guidelines, the PTO has determined that the written description requirement can be met by "show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." Guidelines, 66 Fed. Reg. at 1106 (emphasis added). For example, the PTO would find compliance with § 112, ¶ 1, for a claim to an "isolated antibody capable of binding to antigen X," notwithstanding the functional definition of the antibody, in light of "the art-recognized method of making antibodies *to* fully characterized antigens, the well defined structural

characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that the antibody technology is well developed and mature." Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines").

The general principle of the written description requirement for a claimed genus may be satisfied through (1) sufficient description of a representative number of species by actual reduction to practice, (2) reduction to drawings of a general structure, or (3) disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, (4) describing functional characteristics coupled with a known or disclosed correlation between function and structure, or (5) a combination of such identifying characteristics, sufficient to show the appellant was in possession of the claimed genus (emphasis added). Reagents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

What is claimed here, however, is not a genus of compounds, as in the cases at issue, but a method which encompasses the use of any of an inhibitor within a class of compounds.

The Specification

The specification clearly discloses the proteins to be inhibited - there is no argument in this respect. The basis of the rejection is that the examiner says that the only inhibitor of an anticoagulant disclosed in the specification is an *antibody* which binds the anticoagulant recited in the claims. If this were the case, the fact that antibodies to the other proteins were also available when this application was filed should support claims not just to an antibody to protein

C, but antibodies to the other claimed anticoagulants (see, for example, *J. Histochem. Cytochem.*, 1994 (10):1365-1376 [anti-thrombin III antibody]; *Hybridoma*, 1991(5)633-640 [anti-thrombin III antibody]; *J. Heart Lung Transpant.* 1992(2 pt. 1):342-347 [anti-thrombin III antibody]; *J. Histochem. Cytochem.*, 1994(10):1365-1376 [anti-thrombin III antibody]; *J. Chromatography*, 1991(2):493-500 [heparin cofactor II antiserum]; *Thromb. Haemost* 1992(5):507-509 [thrombomodulin antibodies]; *Kidney Int.*, 1992(5):1170-1174 [thrombomodulin antibodies]; and *Thromb. Haemost.*, 1992(3):310-314 [tissue factor pathway inhibitor antibody]). However, as demonstrated by the enclosed abstracts, other inhibitors of clotting protein were known and could therefore be used in the claimed method (see, for example, *Gene*, 1993, 137(1):25-31 [inhibition of thrombin *via* single stranded DNA oligonucleotides] in combination with *Seminars in Hematology*, Vol. 29 (3):159-169, 1992).

This clotting cascade and its enzymatic components are well characterized (for example, see enclosed *Seminars in Hematology*, Vol. 29 (3):159-169, 1992, by Broze, G.J.). Tissue factor pathway *inhibitor*, already known as playing significant role *in vivo* in regulating coagulation, is taught as playing a role in bacterial sepsis and the regulation of the inflammatory response (*J. Clin. Invest.*, 1993, 91(6):2850-2856). The serine protease, thrombin, has been used as a target for inhibition *via* single stranded DNA oligonucleotides (*Gene*, 1993, 137(1):25-31). Autoantibodies have been shown to inhibit thrombomodulin-mediated protein C activation (*B. J. Haematol.*, 1993, 85(4):761-768). These are just a few examples of compounds that influence the overall activity of the coagulation cascade. In view of known compounds, such as these, the specification, and assays readily available (see, for example, *Thromb. Haemost*, 1993, 70(3):

448-453), one of ordinary skill in the art would have no problem realizing that the Applicant is in possession of the method as claimed.

Not only are a variety of inhibitors known, but each of the claimed anticoagulants (protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor) are well characterized, as taught at pages 4-12 in the specification. In the foregoing section, discussing the legal standard for written description, the Applicant re-iterated the USPTO's clearly stated section for applying the written description guidelines, wherein "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigens were implicitly disclosed *as a result of the isolation of antigen X*." (emphasis added) Synopsis of Application of Written Description Guidelines, at 60, available at http://www.uspto.gov/web/patents/guides.htm ("Application of Guidelines"). Therefore, applicant is entitled to broadly claim the inhibitors of these proteins since these would be readily available to those skilled in the art.

There is no legal requirement for actual reduction to practice of a representative number of species. In view of the isolation of, and well characterized, anti-coagulation factors (protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor), the Applicant submits that this is analogous, to the "isolation of antigen X". This, in combination with the recognized spectrum of antibodies and other compounds which bind to coagulation factors (and the well recognized modes of production of antibodies and well known clotting assays), and the arguments presented in the foregoing paragraphs, provide for a written description which meets the legal requirements under 35 U.S.C. § 112, first paragraph.

Allowance of claims 1-9, 11-13, and 19-21 is respectfully solicited.

Respectfully submitted,

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Certificate of Mailing Under 37 C.F.R. § 1.8(a)

I hereby certify that this paper, along with any paper referred to as being attached or enclosed, is being deposited with the United States Postal Service on the date shown below with sufficient postage as first-class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.

Aisha Wyatt

Date: September 23, 2002

Marked Up Version of Claims as Amended
Pursuant to 37 C.F.R. § 1.121(c)(1)(ii)

1. (three times amended) A method for inhibiting microvascular bleeding at a site in a patient exhibiting microvascular bleeding comprising administering to the patient a compound in a pharmaceutically acceptable carrier in an effective amount to prevent anticoagulation by greater than 90% of activated protein C in human plasma, wherein the compound is an inhibitor of an anticoagulant selected from the group consisting of protein C, antithrombin III, heparin cofactor II, thrombomodulin and tissue factor pathway inhibitor.

2. The method of claim 1 wherein the anticoagulant is protein C.

3. (amended) The method of claim 1 wherein the [antibody] inhibitor is administered systemically.

4. The method of claim 1 wherein the inhibitor is administered topically.

5. The method of claim 1 further comprising topically administering at the site of the bleeding a coagulant.

6. The method of claim 5 wherein the coagulant is selected from the group consisting of thrombin and tissue thromboplastin.

7. The method of claim 2 wherein the inhibitor is an antibody to protein C.

8. (Two times amended) The method of claim 7 wherein the inhibitor is administered systemically further comprising the step of topically administering a coagulant at the site of bleeding.

9. The method of claim 8 wherein the topically administered coagulant is selected from the group consisting of thrombin in a dosage of between approximately 1000 and 10,000 units and tissue factor in a dosage of between approximately 0.1 and 10 mg.

11. (Amended) The method of claim 1 wherein the inhibitor is administered to a burn patient.

MARKED UP VERSION OF AMENDMENTS PURSUANT TO 37 C.F.R. § 1.121

12. (Amended) The method of claim 1 wherein the inhibitor is administered to a patient with tissue or skin grafts.

13. (Amended) The method of claim 1 wherein the inhibitor is administered to a patient with cerebral contusions.

19. The method of claim 4 further comprising the step of topically administering a coagulant at the site of bleeding.

20. The method of claim 3 wherein the inhibitor is a monoclonal antibody immunoreactive with protein C and blocking protein C activation.

21. The method of claim 20 wherein the inhibitor is HPC-4, deposited with the American Type Culture Collection, Rockville, MD and assigned ATCC No. 9892.